CLAIMS

What is claimed is:

1. A method of altering the NAD-dependent acetylation status of at least one amino acid residue in a histone protein by altering the activity of a Sir2 protein.

2. The method of Claim 1, wherein the histone protein is selected from the group consisting of an H2B, H3 or H4 histone protein.

3. The method of Claim 1, wherein the amino acid residue is a lysine amino acid residue.

4. The method of Claim 3, wherein the lysine amino acid residue is lysine 9 and/or lysine 14 of an H3 histone protein.

5. The method of Claim 3, wherein the lysine amino acid residue is lysine 16 of an H4 histone protein.

6. The method of Claim 1, wherein the alteration in NAD-dependent acetylation status is removal of an acetyl group.

7. The method of Claim 1, wherein the Sir2 protein is a Sir2α protein.

8. The method according to Claim 7, wherein the Sir2α protein has the amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 4, 9, 12, 19 or 26.

9. The method according to Claim 7, wherein the Sir2α protein is encoded by the nucleic acid sequence of SEQ ID NO: 25.

10. The method of Claim 7, wherein the Sir2α protein is a mutant Sir2α protein selected from the group consisting of G253A, G255A, S257A, I262A, F265A, R266A, G270A, P285A, T336A, H355A, Thr-261, Iso-271, Arg-275 or Asn-345.

11. A method of identifying an agent which alters the activity of a Sir2 protein by assessing the ability of the agent to alter the NAD-dependent acetylation status of at least one amino acid in a histone protein, comprising the steps of:

(a) combining the histone protein, the Sir2 protein, NAD compound and the agent to be tested, thereby producing a combination;

(b) detecting the NAD-dependent acetylation status of an amino acid in the histone protein in the combination; and

(c) comparing the NAD-dependent acetylation status of an amino acid in the histone protein in the combination with the NAD-dependent acetylation status of the amino acid in the histone protein in the absence of the agent to be tested,

wherein a difference in the NAD-dependent acetylation status of the amino acid of the histone protein in the presence of the agent as compared with the absence of the agent indicates that the agent alters the NAD-dependent acetylation status of at least one amino acid of the histone protein.

12. The method of Claim 11, wherein the agent is an agonist of the activity of the Sir2 protein.

13. The method of Claim 11, wherein the agent is an antagonist of the activity of the Sir2 protein.

14. The method of Claim 11, wherein the alteration of NAD-dependent acetylation status is removal of an acetyl group.

15. The method of Claim 11, wherein the histone protein is selected from the group consisting of an H2B, H3 or H4 histone protein.

16. The method of Claim 11 wherein the NAD-dependent acetylation in the histone protein is acetylation of a lysine amino acid residue.

17. The method of Claim 16, wherein the lysine amino acid residue is lysine 9 and/or lysine 14 of an H3 histone protein.

18. The method of Claim 16, wherein the lysine amino acid residue is lysine 16 of an H4 histone protein.

19. The method of Claim 11, wherein the Sir2 protein is a Sir2α protein.

20. The method of Claim 11, wherein the detecting step is performed by electron-spray mass spectroscopy.

21. A method of identifying an agent which alters life span of a cell by assessing the ability of the agent to alter NAD-dependent acetylation status of at least one amino acid in a histone protein, comprising the steps of:

(a) combining the histone protein, a Sir2 protein, a NAD compound and the agent to be tested, thereby producing a combination;

(b) detecting the NAD-dependent acetylation status of an amino acid in the histone protein in the combination; and

(c) comparing the NAD-dependent acetylation status of an amino acid in the histone protein in the combination with the acetylation status of the amino acid in the histone protein in the absence of the agent to be tested, wherein a difference in the acetylation status of the amino acid of the histone protein in the presence of the agent as compared with the acetylation status of the amino acid of the histone protein in the absence of the agent indicates that the agent alters the life span of the cell.

22. The method of Claim 21, wherein the histone protein is selected from the group consisting of an H2B, H3 or H4 histone protein.

23. The method of Claim 21, wherein the Sir2 protein is a Sir2α protein.

24. The method of Claim 21, further comprising administering to a cell the agent identified by the method and assessing the NAD-dependent acetylation status of at least one amino acid in a histone protein of the cell.

25. A method of altering the NAD-dependent acetylation status of at least one amino acid residue in a histone protein comprising combining the histone protein, a Sir2 protein and a NAD compound.

26. The method of Claim 25, wherein the histone protein is selected from the group consisting of an H2B, H3 or H4 histone protein.

27. The method of Claim 25, wherein the Sir2 protein is a Sir2α protein.

28. A method of identifying an agent which alters mono-ADP-ribosylation of a nuclear protein in a cell, comprising the steps of:

a) combining a cell and an agent to be tested;

b) determining a level of mono-ADP-ribosylation of a nuclear protein in said cell; and

c) comparing the level determined in step (b) with a level of mono-ADP-ribosylation of the nuclear protein in the absence of the agent to be tested,

wherein a difference in the level of mono-ADP-ribosylation of the nuclear protein between the presence of the agent and the absence of the agent indicates that the agent alters mono-ADP-ribosylation of the nuclear protein.

29. The method according to Claim 28, wherein the nuclear protein is a histone protein.

30. The method according to Claim 28, wherein the mono-ADP-ribosylation is performed by a Sir2 protein.

31. The method according to Claim 30, wherein the mono-ADP-ribosylation is performed by a Sir2α protein.

32. A method of identifying an agent which alters life span of a cell, comprising the steps of:

a) combining a cell and an agent to be tested;

b) determining a level of mono-ADP-ribosylation of a nuclear protein in said cell; and

c) comparing the level determined in step (b) with a level of mono-ADP-ribosylation of the nuclear protein in the absence of the agent to be tested,

wherein a difference in the level of mono-ADP-ribosylation of the nuclear protein between the presence of the agent and the absence of the agent indicates that the agent alters the life span of the cell.

33. The method according to Claim 32, wherein the nuclear protein is a histone protein.

34. The method according to Claim 32, wherein the mono-ADP-ribosylation is performed by a Sir2 protein.

35. The method according to Claim 34, wherein the mono-ADP-ribosylation is performed by a Sir2α protein.

~~36.~~ A method of identifying an agent which alters aging of a cell, comprising the steps of:

a) combining a cell and an agent to be tested;

b) determining a level of mono-ADP-ribosylation of a nuclear protein in said cell; and

c) comparing the level determined in step (b) with a level of mono-ADP-ribosylation of the nuclear protein in the absence of the agent to be tested,

wherein a difference in the level of mono-ADP-ribosylation of the nuclear protein between the presence of the agent and the absence of the agent indicates that the agent alters aging of the cell.

37. The method according to Claim 36, wherein the nuclear protein is a histone protein.

38. The method according to Claim 36, wherein the mono-ADP-ribosylation is performed by a Sir2 protein.

~~39.~~ A method of increasing the life span of a cell, comprising administering to the cell an effective amount of an agent which increases mono-ADP-ribosylation of a

nuclear protein, wherein said agent is identified by a method comprising the steps of:

a) combining a cell and an agent to be tested;

b) determining a level of mono-ADP-ribosylation of a nuclear protein in said cell; and

c) comparing the level determined in step (b) with a level of mono-ADP-ribosylation of the nuclear protein in the absence of the agent to be tested,

wherein in the presence of the agent there is an increase in the level of mono-ADP-ribosylation of the nuclear protein.

40. The method according to Claim 39, wherein the nuclear protein is a histone protein.

41. The method according to Claim 39, wherein the mono-ADP-ribosylation is performed by a Sir2 protein.

42. The method according to Claim 39, wherein the agent is selected from the group consisting of a SIR2 protein, a mono-ADP-ribosyltransferase, an agonist of a SIR2 protein, an agonist of a mono-ADP-ribosyltransferase or combinations thereof.

43. A method of decreasing aging of a cell, comprising administering to the cell an effective amount of an agent which increases mono-ADP-ribosylation of a nuclear protein, wherein said agent is identified by a method comprising the steps of:

a) combining a cell and an agent to be tested;

b) determining a level of mono-ADP-ribosylation of a nuclear protein in said cell; and

c) comparing the level determined in step (b) with a level of mono-ADP-ribosylation of the nuclear protein in the absence of the agent to be tested,

wherein in the presence of the agent there is an increase in the level of mono-ADP-ribosylation of the nuclear protein.

44. The method according to Claim 43, wherein the nuclear protein is a histone protein.

45. The method according to Claim 43, wherein the mono-ADP-ribosylation is performed by a Sir2 protein.

~~46.~~ A method of increasing the life span of a cell comprising administering to the cell a mono-ADP-ribosyltransferase or an agonist of a mono-ADP-ribosyltransferase in an amount effective to increase the life span of the cell.

47. The method according to Claim 46, wherein the mono-ADP-ribosyltransferase is a Sir2 protein.

48. The method according to Claim 47, wherein the mono-ADP-ribosyltransferase is a SIR2α protein.

49. The method according to Claim 47, wherein the SIR2 protein comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 4, 9, 12, 19, or 26.

50. The method according to Claim 47, wherein the SIR2 protein is encoded by a nucleic acid sequence of SEQ ID NO: 25.

~~51.~~ A method of increasing the life span of a cell comprising administering to the cell an agonist of mono-ADP-ribosylation of histones H2B, H3 or H4 or combinations thereof in an amount effective to increase the life span of the cell.

52. A method of decreasing aging of a cell comprising administering to the cell a mono-ADP-ribosyltransferase or an agonist of a mono-ADP-ribosyltransferase in an amount effective to decrease aging of the cell.

53. A method of decreasing aging of a cell comprising administering to the cell an agonist of mono-ADP-ribosylation of a histone H2B in an amount effective to decrease aging of the cell.

54. A method of inhibiting formation, replication and/or accumulation of rDNA circles in a cell comprising administering to the cell a mono-ADP-ribosyltransferase or an agonist of a mono-ADP-ribosyltransferase in an amount effective to inhibit the formation, replication and/or accumulation of rDNA circles.

55. A method for decreasing recombination between rDNA in a cell comprising administering to the cell a mono-ADP-ribosyltransferase or an agonist of a mono-ADP-ribosyltransferase in an amount effective to decrease recombination between rDNA.

56. An isolated murine Sir2 protein.

57. Isolated murine Sir2 protein of Claim 56, wherein the murine Sir2 protein is a Sir2α protein.

58. Isolated murine Sir2α protein of Claim 57, wherein the Sir2α protein has the amino acid sequence of SEQ ID NO: 26.

59. Isolated murine Sir2α protein of Claim 57, wherein the Sir2α protein is encoded by the nucleic sequence of SEQ ID NO: 25.

60. A recombinant host cell comprising an isolated nucleic acid molecule of a murine SIR2 gene operably linked to a regulatory sequence.

61. An antibody, or an antigen-binding fragment thereof, which selectively binds a murine Sir2 protein or a murine protein.